Application No.: 10/617159 Docket No.: 023435.0101PTUS

REMARKS

In an Office Action dated 04 August 2005, the Examiner noted that the listing of references in the specification is not a proper information disclosure statement, noted that the Abstract is longer than 150 words and includes legal phraseology "said;" noted typographical errors in the specification; noted the location of the brief description of the figures; objected to Claim 12 as depending on Claim 7 not Claim 1; rejected Claims 13 and 14 under 35 U.S.C. §102(b) as being anticipated by Callahan et al.; rejected Claims 1, 2, 3, 6, 15, 16, 18, and 19 under 35 U.S.C. §102(e) as being anticipated by Glass et al.; requested confirmation regarding subject matter being commonly owned; rejected Claims 7, 8, 9, and 12 under 35 U.S.C. §103(a) as being unpatentable over Glass et al.; and rejected Claims 4, 5, 10, 11, and 17 under 35 U.S.C. §103(a) as being unpatentable over Glass et al. in view of Callahan et al.

Applicants have carefully reviewed the Examiner's rejections and correspondingly the Applicants provide the following remarks regarding same.

Information Disclosure Statement

Applicants have amended the specification to delete the listing of references and they will be included in a later-filed IDS in accordance with 37 CFR 1.98.

Specification

The Examiner further noted that the Abstract contains improper language, legal phraseology, and is longer than 150 words. Applicants have amended the Abstract for proper language, phraseology, and length. Therefore, it is believed that the Applicants have overcome this objection.

The Examiner objected to the disclosure due to informalities. Applicants have reviewed and amended the disclosure to clarify those informalities found. Therefore, it is believed that the Applicants have overcome this objection.

The Examiner noted the location of the brief description of the figures does not comport with the preferred layout for the specification of a utility application. Applicants have amended the specification by adding the paragraph titled "Brief Description of the Drawings" just

before the paragraph titled "Detailed Description of the Preferred Embodiments." Therefore, it is believed that the Applicants have overcome this objection.

Claim Objections

The Examiner objected to Claim 12 on his belief that it is dependent upon Claim 7 and not Claim 1. Applicants have amended Claim 12 to clarify that it is dependent upon Claim 7. Therefore, it is believed that the Applicants have overcome this objection.

Claim Rejections – 35 U.S.C. §102

The Examiner rejected Claims 13 and 14 under 35 U.S.C. §102(b) as being anticipated by Callahan et al. (6,324,423B1). The Applicants respectfully traverse the Examiner's rejection of Claims 13 and 14 under 35 U.S.C. §102(b) as being anticipated by Callahan et al. (6,324,423B1). With regards to Claims 13 and 14, the Examiner noted:

> Callahan et al. disclose a method involving providing a drug to a subject (col. 4, line 6), collecting beat-to-beat data representing a cardiac interval (col. 3, line 67), defining bins with value ranges (col. 4, line 1), organizing data into bins to create a composite histogram and statistically analyzing the composite histogram after exposure to the drug (Fig. 16).

Applicants respectfully disagree with the Examiner's conclusions. In particular, the Callahan reference does not disclose or teach any reference to a particular subject's QT interval histograms being compared before and after administration of a drug. Callahan does teach comparing QT interval histograms of normal subjects, subjects with long QT syndrome, and drug titration studies.

Further, the Callahan reference does not teach any reference to the use of a composite histogram that merges many patients' data into a composite data set or "population," from which a mean and standard deviation is calculated. Additionally, the Callahan reference does not teach comparing two or more populations against each other to check for statistical differences between two or more populations, nor does it teach comparing a population composite histogram against a single patient's binned histogram to determine what population (e.g. normal, congenital disorder, or drug-induced damaged) that particular patient belongs. Thus, the Callahan reference does not teach or disclose using a composite histogram as described above. (Pg. 19, First Paragraph)

In addition, the Callahan reference teaches bear-to-beat binning of QT and QTc intervals, but is limited to the analysis of only the outliers by calculating the percent of beats that exceed a certain threshold from the collected data set. Furthermore, the Callahan reference does not teach a method to analyze central tendency, skewness, shape of histograms, variance, kurtosis, or other statistical properties of the histogram as appropriate for Gaussian or non-Gaussian distributions as disclosed in Applicants' application. (See Figures 1 – 6)

For example, Figure 6 shows the comparison between a composite histogram for a patient with congenital QT syndrome and a set of normal data, the comparison showing that a Student t-test proves that the likelihood of the patient's histogram was sampled from the same population set as the normal was less than one in a million. The sharpness and conclusiveness of these results shows the improvement of Applicants' application over a standard 12-lead ECG, which does not provide for the bear-to-beat dynamicity of the QT_c interval. Figure 6 further shows how Applicants' application is an effective diagnostic test in that it provides a quantitative comparison of two or more sets of QT and QT_c intervals, such as for comparison of a group of patients before and after a drug treatment. It also provides application of a variety of statistical methods to define whether two or more sets of intervals are different.

Applicants have amended Claim 13 to clarify that the subject's composite histogram is compared with a composite histogram for a group of subjects that are not provided the pharmaceutical or other therapeutic agent. This element is not taught or disclosed by the Callahan reference. In addition, the Applicants have amended Claim 14 to clarify that the Callahan reference does not teach each and every element of Claims 13 and 14 of the present application. Thus, the cited Callahan reference fails to meet all the elements recited and claimed in Claims 13 and 14, and Applicants believe that Claims 13 and 14 are allowable under 35 U.S.C. §102(b) over the Callahan reference.

The Applicants respectfully traverse the Examiner's rejection of Claims 1, 2, 3, 6, 15, 16, 18, and 19 under 35 U.S.C. §102(e) as being anticipated by Glass et al. (2005/0165320), as the Examiner noted:

> Glass et al. disclose a method for detecting cardiac arrhythmia based on comparing a subject's histogram with composite histograms of R-R intervals after exposure to a drug (par. 0012). In regards to claims 16 and 18, the individual histogram is compared to a set of subjects who are "normal"

for a given R-R interval to determine if the individual is from the group used to construct the composite curve. In regards to claim 19, the composite curves are derived from subjects with baseline characteristics and the individual histogram is derived from a potentially normal subject.

Applicants respectfully disagree with the Examiner's conclusions. In particular, the Glass reference teaches detecting blocks of successive R-R intervals among a larger data set of R-R values for an individual subject and then calculating a mean value for these blocks. A typical block size is taught as comprising 100 successive R-R intervals. In calculating the mean value, the blocks of individual R-R intervals are averaged, which minimizes the understanding of the beat-to-beat variability inherent in interval data. (Paragraph 0047) The mean value for each calculated block is then identified as falling into one of sixteen different classes, each class consisting of a range of time for a particular histogram. Each block's mean value is then plotted on the histogram consistent with the incremental R-R intervals for each individual subject. A standard R-R probability density histogram is then compiled by lumping data together from all the subjects in the group. (Paragraph 0047) Next, Glass teaches generating similarly a histogram for a particular test patient and then comparing the test patient's histogram to the standard histogram to determine whether the subject has experienced atrial fibrillation. (Paragraphs 0047 – 0052)

It is well known among those skilled in the art that QT intervals undergo significant changes over both the short and long term due to circadian rhythms and autonomic control. (See Applicants' Description, Page 10, Last Para.; Page 11, 2nd Para.) By averaging the data collected for generating the standard histogram and the patient's histogram, the beat-to-beat variability inherent in QT interval data is minimized. Further, the averaging of data may obscure these significant short-term variations in QT intervals.

Conversely, the Applicants' application discloses and claims, in part, collecting individual beat-to-beat QT intervals from high-resolution AECGs, defining a plurality of bins, organizing each of the collected beat-to-beat data into one of the plurality of bins to create a histogram, constructing a composite histogram by summing the contents of each bin from a set of individual histograms derived from a group of recording taken from several individuals with common characteristics, and performing statistical analysis on the combined histogram to define the statistical characteristics of the group. (See Claim 1) The Applicants' application discloses and claims placing each individual QT interval into a bin so that the beat-to-beat measurements retain the natural variability data that

may be important for calculating a patient's risk of dysrhythmia and sudden death. (See Applicants' Description, Pg. 11, 4th Para.)

The Glass reference does not teach each and every element of Applicants' application; specifically, the Glass reference does not teach or claim Applicants' limitation, "organizing each of the collected beat-to-beat data into one of the plurality of bins in accordance with the value of the data and the value range of the bin to create a histogram." (See Applicants' amended Claim 1) Since the Glass reference averages the blocks of 100 individual R-R intervals to produce a mean value, it minimizes the beat-to-beat variability of the individual QT intervals as disclosed and claimed in Applicant's Claim 1. Thus, the cited Glass reference fails to meet all the elements recited in Applicants' amended independent Claim 1, and Applicants believe that Claim 1 and corresponding amended independent Claim 15 are allowable under 35 U.S.C. §102(e) over the Glass reference. Applicants also believe that dependent claims 2, 3, 6, 16, 18, and 19 are also allowable under 35 U.S.C. §102(e) over the Glass reference, since these claims depend on allowable base claims.

Claim Rejections – 35 U.S.C. §103(A)

Regarding the Examiner's mention of the duty under 37 CFR 1.56, Applicants confirm that the subject matter of the various claims was commonly owned at the time of the inventions covered therein.

The Applicants respectfully traverse the Examiner's rejection of Claims 7, 8, 9, and 12 under 35 U.S.C. §103(a) as being unpatentable over Glass et al. (2005/0165320), as the Examiner noted:

> Glass et al. substantially disclose the claimed invention except for comparing a histogram from one group of subjects to another histogram from another group of subjects. It is well known in the art to compare characteristics, such as means, standard deviations, and histograms of two groups to determine if they are from the same population. Therefore, it would have been obvious to one having ordinary skill in the art at the time of invention to use two composite histograms to determine if two groups are from the same population.

The Glass reference does not teach each and every element of Applicants' application; specifically, the Glass reference does not teach or claim Applicants' limitation, "organizing each of

the collected beat-to-beat data into one of the plurality of bins in accordance with the value of the data and the value range of the bin to create a histogram." (See Applicants' amended Claim 1) Since the Glass reference averages the blocks of 100 individual R-R intervals to produce a mean value, it minimizes the beat-to-beat variability of the individual QT intervals as disclosed and claimed in Applicant's Claim 1. Thus, the cited Glass reference fails to meet all the elements recited in Applicants' amended independent Claim 7, and Applicants believe that Claim 7 is allowable under 35 U.S.C. §103(a) over the Glass reference. Applicants also believe that dependent claims 8, 9, and 12 are also allowable under 35 U.S.C. §103(a) over the Glass reference, since these claims depend on allowable base claims.

The Applicants respectfully traverse the Examiner's rejection of Claims 4, 5, 10, 11, and 17 under 35 U.S.C. §103(a) as being unpatentable over Glass et al. (2005/0165320) in view of Callahan et al., as the Examiner noted:

> Glass et al. disclose the essential features of the claimed invention except for an interval measurement comprising an amplitude measurement, obtaining an ambulatory ECG recording, and comparing an individual histogram to a placebo histogram. Callahan et al. teach of measuring an amplitude to create histograms based on variables other than time (claim 4), using an ambulatory ECG recording device to allow long-term ECG recording outside of a clinical environment (claim 5), and comparing an individual histogram to a placebo histogram to determine the probability that the two groups are the same (col. 9, line 17). Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention to measure an amplitude to create histograms based on variables other than time, use an ambulatory ECG recording device to allow long-term ECG recording outside of a clinical environment, and device to allow long-term ECG recording outside of a clinical environment, and compare an individual histogram to a placebo histogram to determine the probability that the two groups are the same.

As argued above, neither the Glass reference nor the Callahan reference teaches "organizing each of the collected beat-to-beat data into one of the plurality of bins to create a histogram" as found in Applicants' amended independent Claims 1, 7, and 15 from which Claims 4, 5, 10, 11, and 17 respectively depend. Thus, the cited Glass reference and the cited Callahan reference fails to teach all the elements recited in Applicants' amended independent Claims 1, 7, and 15, and Applicants believe that Claims 1, 7, and 15 are allowable under 35 U.S.C. §103(a) over the Glass reference. Applicants also believe that dependent Claims 4, 5, 10, 11, and 17 are also

allowable under 35 U.S.C. §103(a) over the Glass reference in view of the Callahan reference, since these claims depend on allowable base claims.

In view of the above amendments and remarks, Applicants believe the pending application is in condition for allowance. A Petition For Extension Of Time and the corresponding fee are attached. If any additional fee is due, please charge our Deposit Account No. 50-1848, under Order No. 023435.0101PTUS from which the undersigned is authorized to draw.

Respectfully submitted,
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